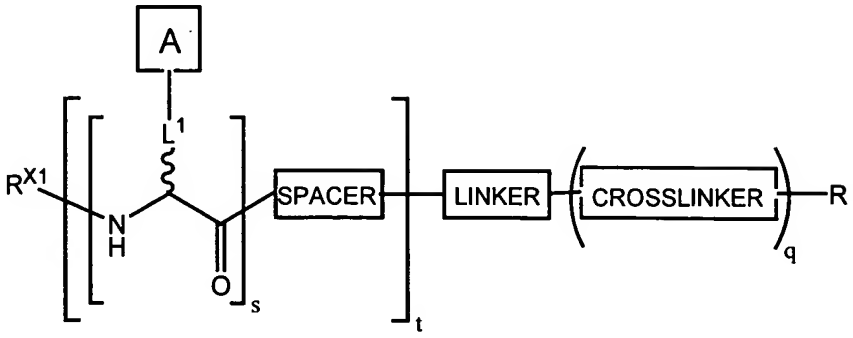
CLAIMS

What is claimed is:

1. A clustered multi-antigenic construct having the structure:



wherein q is 0 or 1;

each occurrence of s is independently an integer from 1-20;

t is an integer from 1-6;

R^{X1} is hydrogen, alkyl, acyl, aryl, heteroaryl, -alkyl(aryl), -alkyl(heteroaryl), a nitrogen protecting group, an amino acid or a proctected amino acid;

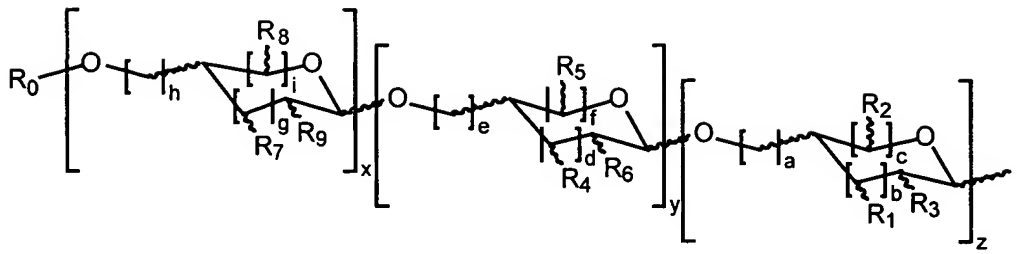
R is hydrogen or an immunogenic carrier;

each occurrence of the spacer is independently a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, heteroaryl or peptidic moiety;

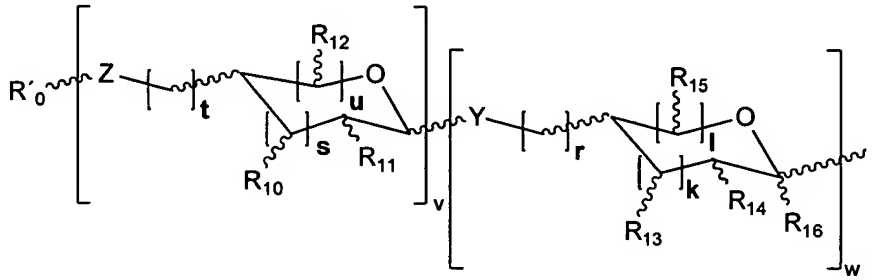
the linker is either a free carboxylic acid, –O-, (carboxamido)alkyl carboxamide, MBS, primary carboxamide, mono- or dialkyl carboxamide, mono- or diarylcarboxamide, linear or branched chain (carboxy)alkyl carboxamide, linear or branched chain (alkoxycarbonyl)alkyl-carboxamide, linear or branched chain (carboxy)arylalkylcarboxamide, linear or branched chain (alkoxycarbonyl)alkylcarboxamide, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester;

each occurrence of L^1 is independently a substituted or unsubstituted aliphatic or heteroaliphatic moiety;

each occurrence of A is independently a carbohydrate determinant having the structure:



wherein a, b, c, d, e, f, g, h, i, x, y and z are independently 0, 1, 2 or 3, with the proviso that the x, y and z bracketed structures represent furanose or pyranose moieties and the sum of b and c is 1 or 2, the sum of d and f is 1 or 2, and the sum of g and i is 1 or 2, and with the proviso that x, y and z are not simultaneously 0; wherein R_0 is hydrogen, a linear or branched chain alkyl, acyl, arylalkyl or aryl group; wherein each occurrence of R_1, R_2, R_3, R_4 , R_5, R_6 , R_7, R_8 and R_9 is independently hydrogen, OH, OR^i, NHR^i, $NHCOR^i$, F, CH_2OH, CH_2OR^i, a substituted or unsubstituted linear or branched chain alkyl, (mono-, di- or tri)hydroxyalkyl, (mono-, di- or tri)acyloxyalkyl, arylalkyl or aryl group; wherein each occurrence of R^i is independently hydrogen, CHO, $COOR^{ii}$, or a substituted or unsubstituted linear or branched chain alkyl, acyl, arylalkyl or aryl group or a saccharide moiety having the structure:



wherein Y and Z are independently NH or O; wherein k, l, r, s, t, u, v and w are each independently 0, 1 or 2; with the proviso that the v and w bracketed structures represent furanose or pyranose moieties and the sum of l and k is 1 or 2, and the sum of s and u is 1 or 2, and with the proviso that v and w are not simultaneously 0; wherein R'_0 is hydrogen, a linear or branched chain alkyl, acyl, arylalkyl or aryl group; wherein each occurrence of R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} is independently hydrogen, OH, OR^{iii}, NHR^{iii}, $NHCOR^{iii}$, F, CH_2OH, CH_2OR^{iii}, or a substituted or unsubstituted linear or branched chain alkyl, (mono-, di- or tri)hydroxyalkyl, (mono-, di- or tri)acyloxyalkyl, arylalkyl or aryl group; wherein each occurrence of R_{16} is hydrogen, COOH, $COOR^{ii}$, $CONHR^{ii}$, a substituted or unsubstituted linear or branched chain

alkyl or aryl group; wherein each occurrence of R^{iii} is hydrogen, CHO, $COOR^{iv}$, or a substituted or unsubstituted linear or branched chain alkyl, acyl, arylalkyl or aryl group; and wherein each occurrence of R^{ii} and R^{iv} are each independently H, or a substituted or unsubstituted linear or branched chain alkyl, arylalkyl or aryl group.

2. The construct of claim 1 wherein t is ≥ 2 and within each bracketed structure s, independently, each occurrence of A is the same.

3. The construct of claim 1, wherein occurrences of A from one bracketed structure s to the next are different.

4. The construct of claim 1, wherein A, for each occurrence, is independently selected from the group consisting of Globo-H, fucosyl GM1, KH-1, glycophorin, N3, Tn, TF, STN, (2,3)ST, 2,6-STn, Gb3, Le^y and Le^x.

5. The construct of claim 1, wherein each occurrence of L^1 is independently a moiety having the structure $-O(CH_2)_n-$ wherein n is an integer from 1-10; or a natural amino acid side chain.

6. The construct of claim 5, wherein each occurrence of L^1 is independently a moiety having the structure $-O(CH_2)_n-$ wherein n is an integer from 1-10.

7. The construct of claim 6, wherein n is 3.

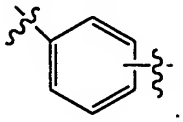
8. The construct of claim 1, wherein each occurrence of L^1 is independently a natural amino acid side chain.

9. The construct of claim 1, wherein R^{XI} is an acyl moiety.

10. The construct of claim 9, wherein R^{XI} is an amino acid residue.

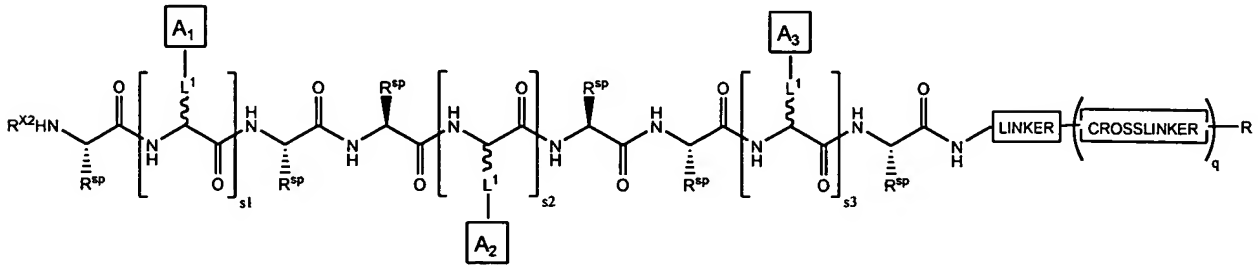
11. The construct of claim 1, wherein the spacer, for each occurrence, is independently a substituted or unsubstituted C_{1-6}alkylidene or C_{2-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; a peptidyl moiety or a bivalent aryl or heteroaryl moiety.

12. The construct of claim 1, wherein the spacer, for each occurrence, is independently $-(CHR^{sp})_n-$, where n is 1-8 and each occurrence of R^{sp} is independently hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, -alkyl(aryl), -alkyl(heteroaryl), $-OR^{sp1}$, $-SR^{sp}1$ or $-NR^{sp1}R^{sp2}$ where R^{sp1} and R^{sp1} are independently hydrogen or lower alkyl; a peptidyl moiety comprising one or more α-amino acid residues, or a bivalent aryl moiety having the structure:



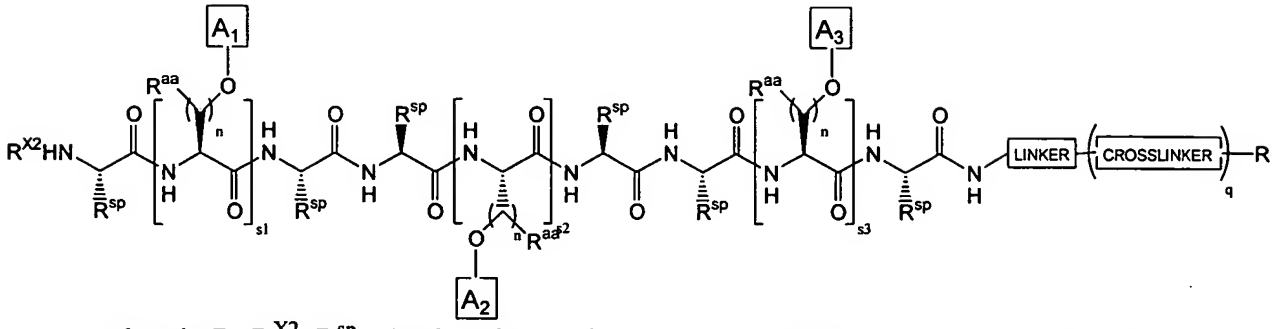
13. The construct of claim 1, wherein each occurrence of the spacer is independently a dipeptidyl moiety.

14. The construct of claim 1, wherein t is 3, each occurrence of the spacer that is not directly attached to the linker is independently a dipeptidyl moiety and the glycopeptide has the structure:



wherein L^1 and R^{sp} are as defined in claim 1; s1, s2 and s3 are independently integers from 2-5; A_1-A_3 are carbohydrate domains, as defined for A in claim 1, and are different from each other; and R^{X2} is hydrogen, alkyl, acyl, aryl, heteroaryl, -alkyl(aryl), -alkyl(heteroaryl) or a nitrogen protecting group.

15. The construct of claim 14 having the structure:



wherein R, R^{X2}, R^{sp}, s1, s2 and s3 and A_1-A_3 are as defined in claim 14; each occurrence of n is independently an integer from *1-10*; and each occurrence of R^{aa} is hydrogen, lower alkyl, aryl, heteroaryl, -alkyl(aryl) or –alkyl(heteroaryl).

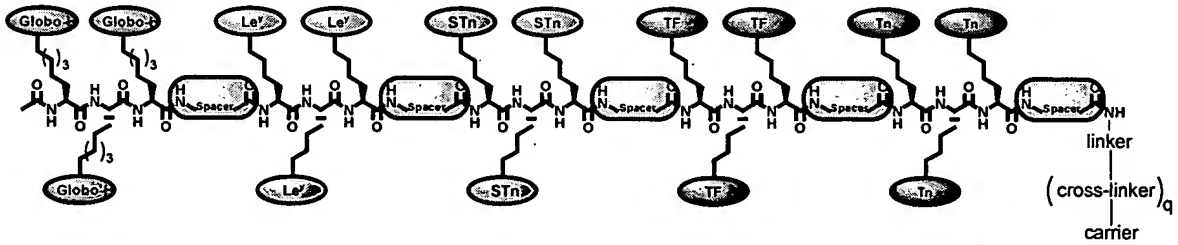
16. The construct of claim 15, wherein each occurrence of n is 1 and each occurrence of R^{aa} is hydrogen or methyl.

17. The construct of claim 15, wherein each occurrence of n is independently an integer from *1-10* and each occurrence of R^{aa} is hydrogen.

18. The construct of claim 15, wherein each occurrence of R^{sp} is independently a natural amino acid side chain.

19. The construct of claim 18, wherein each occurrence of R^{sp} is hydrogen.

20. The construct of claim 1 having the structure:



wherein q

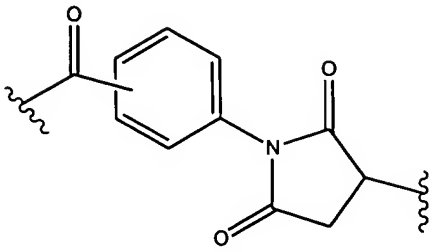
CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl;

a peptidyl moiety or a bivalent aryl or heteroaryl moiety; the linker is either a free carboxylic acid, –O-, (carboxamido)alkyl carboxamide, MBS, primary carboxamide, mono- or dialkyl carboxamide, mono- or diarylcarboxamide, linear or branched chain (carboxy)alkyl carboxamide, linear or branched chain (alkoxycarbonyl)alkyl-carboxamide, linear or branched chain (carboxy)arylalkylcarboxamide, linear or branched chain (alkoxycarbonyl)alkylcarboxamide, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester; and the carrier is an immunogenic carrier.

21. The construct of claim 1, 14, 15 or 20, wherein the linker is -O-, -NR_G-, -NR_G(aliphatic)NR_J-, -NR_G(heteroaliphatic)NR_J-, -(aliphatic)NR_J-, -(heteroaliphatic)NR_J-, -O(aliphatic)NR_J-, -O(heteroaliphatic)NR_J-, -NR_G(aliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, -NR_G(heteroaliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, -(aliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, -(heteroaliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, -O(aliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, -O(heteroaliphatic)NR_J(C=O)$(CR_HR_I)_kS$-, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester, wherein each occurrence of k is independently 1-5; wherein each occurrence of R_G, R_H, R_I or R_J is independently hydrogen, a linear or branched, substituted or unsubstituted, cyclic or acyclic moiety, or a substituted or unsubstituted aryl moiety, and wherein each aliphatic or heteroaliphatic moiety is independently substituted or unsubstituted, linear or branched, cyclic or acyclic.

22. The construct of claim 21, wherein the linker is -O-, -$NR_G(CR_HR_I)_kNR_J$-, -$NR_G(CR_HR_I)_kNR_J(C=O)(CR_HR_I)_kS$-, -$NR_G$-, -$(CR_HR_J)_kNR_I$-, -$O(CR_HR_I)_kNR_J$, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester, wherein each occurrence of k is independently 1-5, wherein each occurrence of R_G, R_H, R_I or R_J is independently hydrogen, a linear or branched, substituted or unsubstituted, cyclic or acyclic moiety, or a substituted or unsubstituted aryl moiety.

23. The construct of claim 1, 14, 15 or 20, wherein q is 1 and the crosslinker is a fragment having the structure:



whereby said structure is generated upon conjugation of maleimidobenzoic acid N-hydroxy succinimide ester with a linker.

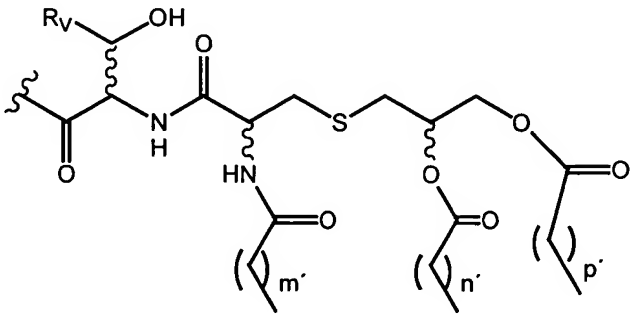
24. The construct of claim 1, 14 or 15, wherein R is hydrogen and q is 0.

25. The construct of claim 1, 14 or 15, wherein R is an immunogenic carrier.

26. The construct of claim 25 wherein the immunogenic carrier is a protein, peptide or lipid.

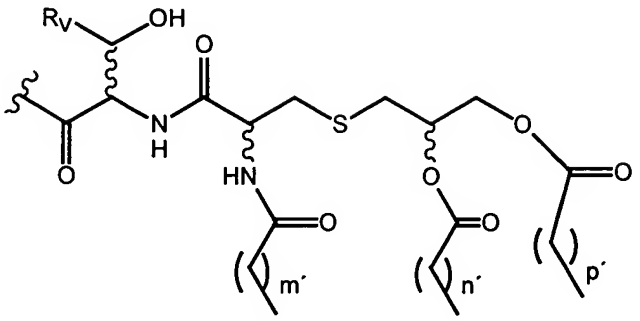
27. The construct of claim 26 wherein the carrier is KLH, polylysine, HSA or BSA.

28. The construct of claim 1, 14 or 15, wherein q is 0 and R is a lipid immunogenic carrier having the structure:



wherein m′, n′ and p′ are each independently integers between about 8 and 20; and R_V is hydrogen, substituted or unsubstituted linear or branched chain lower alkyl or substituted or unsubstituted phenyl.

29. The construct of claim 20, wherein q is 0 and the carrier is a lipid immunogenic carrier having the structure:



wherein m′, n′ and p′ are each independently integers between about 8 and 20; and R_V is hydrogen, substituted or unsubstituted linear or branched chain lower alkyl or substituted or unsubstituted phenyl.

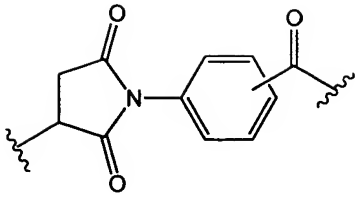
30. The construct of claim 28 wherein m′, n′ and p′ are each 14 and the lipid is tripalmitoyl-S-glycerylcysteinylserine.

31. The construct of claim 1, 14 or 15, wherein each occurrence of A is independently Globo-H, fucosyl GM1, KH-1, glycophorin, Le^y, Le^x, N3, Tn, STN, 2,6-STn, (2,3)ST, Gb3 or TF.

32. The construct of claim 1, 14, 15 or 20, wherein the linker is a moiety having the structure $-NH(CH_2)_tNHC(=O)(CH_2)_vS-$; wherein t and v are each independently integers from 1-6.

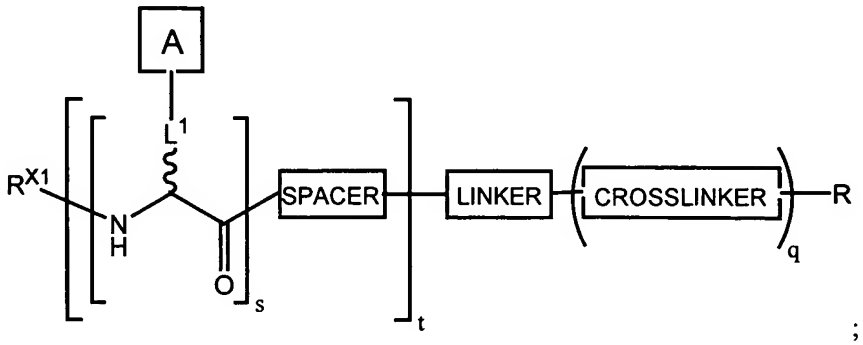
33. The construct of claim 1, 14 or 15, wherein n and q are each 0, R is hydrogen and the linker is a moiety having the structure $-NH(CH_2)_tNHC(=O)(CH_2)_vS-$ wherein t and v are each independently integers from 1-6.

34. The construct of claim 1, 14 or 15, wherein n is 0, q is 1, R is KLH, the linker is a moiety having the structure $-NH(CH_2)_tNHC(=O)(CH_2)_vS-$ wherein t and v are each independently integers from 1-6, and the crosslinker is a moiety having the structure:



35. The construct of claim 32 wherein t is 3 and v is 1.

36. A method for the synthesis of clustered multi-antigenic constructs having the structure:



;

wherein q is 0 or 1;

each occurrence of s is independently an integer from 2-20;

t is an integer from 1-6;

R^{X1} is hydrogen, alkyl, acyl, aryl, heteroaryl, -alkyl(aryl), -alkyl(heteroaryl), a nitrogen protecting group, an amino acid or a proctected amino acid;

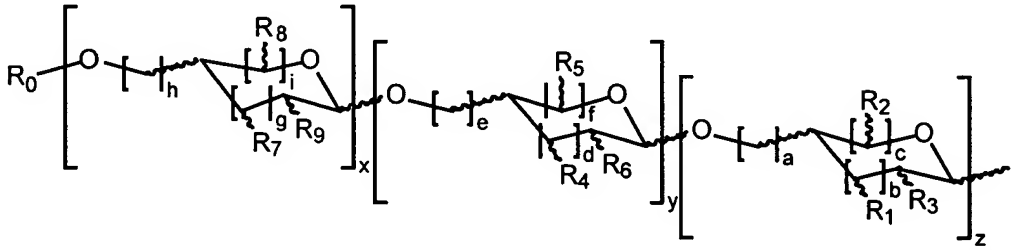
R is hydrogen or an immunogenic carrier;

each occurrence of the spacer is independently a substituted or unsubstituted aliphatic, heteroaliphatic, aryl, heteroaryl or peptidic moiety;

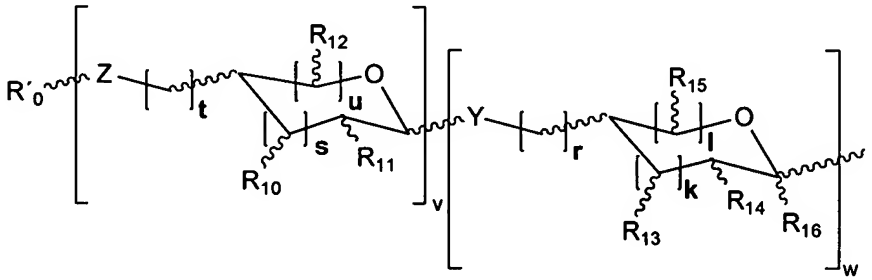
the linker is either a free carboxylic acid, –O-, (carboxamido)alkyl carboxamide, MBS, primary carboxamide, mono- or dialkyl carboxamide, mono- or diarylcarboxamide, linear or branched chain (carboxy)alkyl carboxamide, linear or branched chain (alkoxycarbonyl)alkyl-carboxamide, linear or branched chain (carboxy)arylalkylcarboxamide, linear or branched chain (alkoxycarbonyl)alkylcarboxamide, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester;

each occurrence of L^1 is independently a substituted or unsubstituted aliphatic or heteroaliphatic moiety;

each occurrence of A is independently a carbohydrate domain having the structure:



wherein a, b, c, d, e, f, g, h, i, x, y and z are independently 0, 1, 2 or 3, with the proviso that the x, y and z bracketed structures represent furanose or pyranose moieties and the sum of b and c is 1 or 2, the sum of d and f is 1 or 2, and the sum of g and i is 1 or 2, and with the proviso that x, y and z are not simultaneously 0; wherein R_0 is hydrogen, a linear or branched chain alkyl, acyl, arylalkyl or aryl group; wherein each occurrence of R_1, R_2, R_3, R_4 , R_5, R_6 , R_7, R_8 and R_9 is independently hydrogen, OH, OR^i, NHR^i, $NHCOR^i$, F, CH_2OH, CH_2OR^i, a substituted or unsubstituted linear or branched chain alkyl, (mono-, di- or tri)hydroxyalkyl, (mono-, di- or tri)acyloxyalkyl, arylalkyl or aryl group; wherein each occurrence of R^i is independently hydrogen, CHO, $COOR^{ii}$, or a substituted or unsubstituted linear or branched chain alkyl, acyl, arylalkyl or aryl group or a saccharide moiety having the structure:



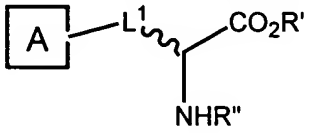
wherein Y and Z are independently NH or O; wherein k, l, r, s, t, u, v and w are each independently 0, 1 or 2; with the proviso that the v and w bracketed structures represent furanose or pyranose moieties and the sum of l and k is 1 or 2, and the sum of s and u is 1 or 2, and with the proviso that v and w are not simultaneously 0; wherein R'_0 is hydrogen, a linear or branched chain alkyl, acyl, arylalkyl or aryl group; wherein each occurrence of R_{10}, R_{11}, R_{12}, R_{13}, R_{14} and R_{15} is independently hydrogen, OH, OR^{iii}, NHR^{iii}, $NHCOR^{iii}$, F, CH_2OH, CH_2OR^{iii}, or a substituted or unsubstituted linear or branched chain alkyl, (mono-, di- or tri)hydroxyalkyl,

(mono-, di- or tri)acyloxyalkyl, arylalkyl or aryl group; wherein each occurrence of R_{16} is hydrogen, COOH, $COOR^{ii}$, $CONHR^{ii}$, a substituted or unsubstituted linear or branched chain alkyl or aryl group; wherein each occurrence of R^{iii} is hydrogen, CHO, $COOR^{iv}$, or a substituted or unsubstituted linear or branched chain alkyl, acyl, arylalkyl or aryl group; and wherein each occurrence of R^{ii} and R^{iv} are each independently H, or a substituted or unsubstituted linear or branched chain alkyl, arylalkyl or aryl group; and wherein each glycosidic moiety is either α- or β-linked to an amino acid;

wherein within each bracketed structure s, independently, each occurrence of A is the same

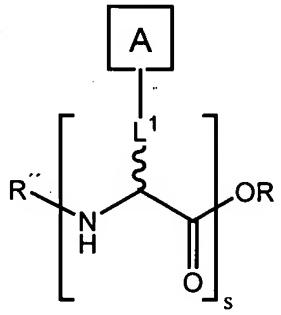
wherein said method comprises steps of:

(a) providing a glycoamino acid having the structure:



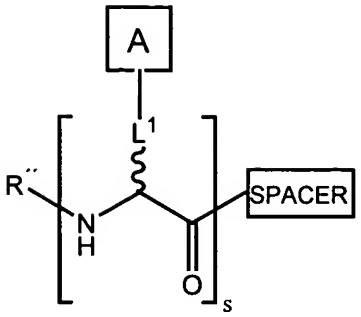
wherein A is a carbohydrate domain as described above;

(b) reacting s occurrences of said glycoamino acid under suitable conditions to generate a glycopeptide having the structure:

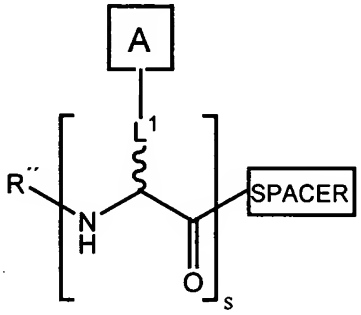


wherein s is an integer from 2-20; each occurrence of A is the same within the bracketed glycopeptide s; R′ is hydrogen or a protecting group; and R′′ is hydrogen, a protecting group, an amino acid or a protected amino acid;

(c) reacting said glycopeptide with a spacer under suitable conditions to generate a spacer construct having the structure:

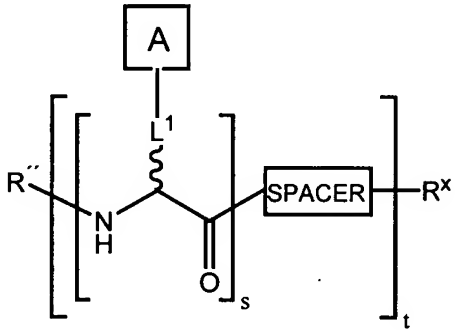


(d) Repeating steps (a) through (c) t-1 times to generate t-1 spacer constructs each independently having the structure:



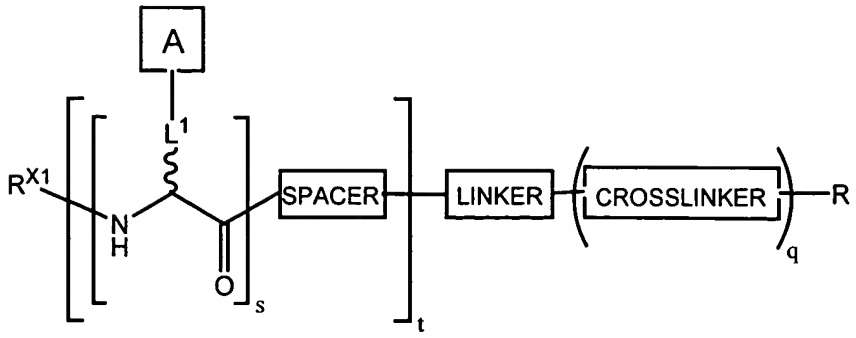
wherein, for each spacer construct, s, L^1, R'' and the spacer moiety may be the same or different; and each spacer construct comprises a different carbohydrate domain A;

(e) Reacting the spacer construct formed in step (c) with the spacer constructs of step (d) under suitable conditions to generate a construct having the structure:



wherein R^x is a protecting group; each occurrence of A is the same within each bracketed structure s; and each bracketed structure s comprises a different carbohydrate domain A; and

(f) Reacting the constructs of step (e) with a linker and optionally a crosslinker and/or an immunogenic carrier under suitable conditions to form the clustered multi-antigenic construct having the structure:



wherein q, linker, crosslinker and R are as defined above.

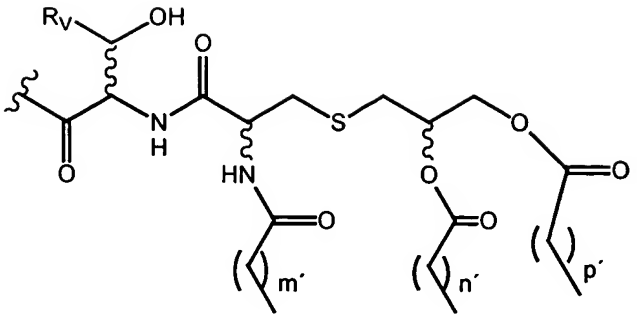
37. A pharmaceutical composition comprising:
a construct of claim 1, and
a pharmaceutically suitable carrier.

38. The pharmaceutical composition of claim 37, wherein the construct is conjugated to an immunogenic carrier.

39. A pharmaceutical composition comprising:
a pharmaceutically acceptable carrier;
an immunogenic carrier; and
a multi-antigenic clustered construct of claim 1;
whereby the construct has not been conjugated to the immunogenic carrier.

40. The pharmaceutical composition of claim 37 or 39, wherein the immunogenic carrier is bovine serum albumin, polylysine or keyhole limpet hemocyanin.

41. The pharmaceutical composition of claim 37 or 39, wherein the construct does not comprise a crosslinker and the immunogenic carrier is a lipid having the structure:



wherein m′, n′ and p′ are each independently integers between about 8 and 20; and R_V is hydrogen, substituted or unsubstituted linear or branched chain lower alkyl or substituted or unsubstituted phenyl.

42. The pharmaceutical composition of claim 41, wherein m′, n′ and p′ are each 14 and the lipid is tripalmitoyl-S-glycerylcysteinylserine.

43. The pharmaceutical composition of claim 37 or 39, further comprising one or more immunological adjuvants.

44. The pharmaceutical composition of claim 43, wherein at least one of said one or more immunological adjuvants is a saponin adjuvant.

45. The pharmaceutical composition of claim 44, wherein the saponin adjuvant is GPI-0100.

46. The pharmaceutical composition of claim 43, wherein at least one of said one or more immunological adjuvants is bacteria or liposomes.

47. The pharmaceutical composition of claim 46, wherein the immunological adjuvant is Salmonella minnesota cells, bacille Calmette-Guerin or QS21.

48. A method of treating cancer in a subject suffering therefrom comprising:
administering to a subject a therapeutically effective amount of a clustered multi-antigenic construct of claim 1,

and a pharmaceutically suitable carrier.

49. The method of claim 48, wherein the construct is conjugated to an immunogenic carrier.

50. The method of claim 48, wherein the construct has not been conjugated to a carrier, and the method further comprises administering an immunogenic carrier.

51. The method of claim 48, wherein said method comprises preventing the recurrence of cancer in a subject.

52. The method of claim 48 or 51, wherein the cancer is a solid tumor.

53. The method of claim 48 or 51, wherein the subject is in clinical remission, or where the subject has been treated by surgery, has limited unresected disease.

54. A method of inducing antibodies in a subject, wherein the antibodies are capable of specifically binding with tumor cells, which comprises administering to the subject an amount of a clustered multi-antigenic construct of claim 1 effective to induce the antibodies.

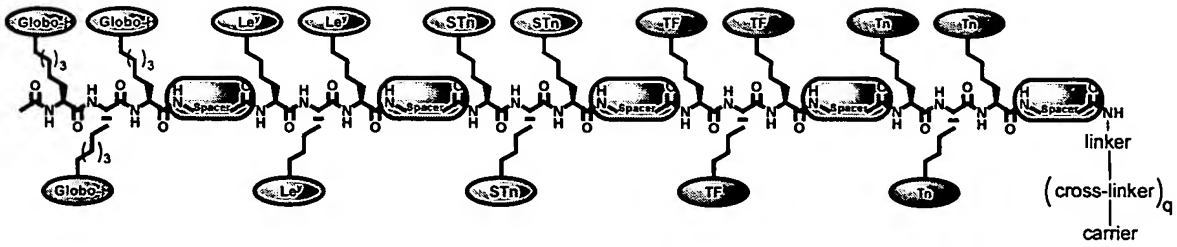
55. The method of claim 54, wherein the glycopeptide is conjugated to an immunogenic carrier.

56. A method of inducing antibodies in a subject, wherein the antibodies are capable of specifically binding with tumor cells, which comprises administering to the subject:

an amount of a clustered multi-antigenic construct of claim 1; wherein R is hydrogen; and wherein the amount of construct is effective to induce the antibodies.

57. The method of claim 56, wherein the method further comprises administering an immunogenic carrier.

58. The method of claim 48, 54 or 56, wherein the clustered multi-antigenic construct has the stucture:



wherein q is 0 or 1; the spacer, for each occurrence, is independently a substituted or unsubstituted C_{1-6}alkylidene or C_{2-6}alkenylidene chain wherein up to two non-adjacent methylene units are independently optionally replaced by CO, CO_2, COCO, $CONR^{Z1}$, $OCONR^{Z1}$, $NR^{Z1}NR^{Z2}$, $NR^{Z1}NR^{Z2}CO$, $NR^{Z1}CO$, $NR^{Z1}CO_2$, $NR^{Z1}CONR^{Z2}$, SO, SO_2, $NR^{Z1}SO_2$, SO_2NR^{Z1}, $NR^{Z1}SO_2NR^{Z2}$, O, S, or NR^{Z1}; wherein each occurrence of R^{Z1} and R^{Z2} is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl or acyl; a peptidyl moiety or a bivalent aryl or heteroaryl moiety; the linker is either a free carboxylic acid, –O-, (carboxamido)alkyl carboxamide, MBS, primary carboxamide, mono- or dialkyl carboxamide, mono- or diarylcarboxamide, linear or branched chain (carboxy)alkyl carboxamide, linear or branched chain (alkoxycarbonyl)alkyl-carboxamide, linear or branched chain (carboxy)arylalkylcarboxamide, linear or branched chain (alkoxycarbonyl)alkylcarboxamide, an oligoester fragment comprising from 2 to about 20 hydroxy acyl residues, a peptidic fragment comprising from 2 to about 20 amino acyl residues, or a linear or branched chain alkyl or aryl carboxylic ester; and the carrier is an immunogenic carrier